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Immune Deficiency and Risk for Malignancy Among Persons with AIDS

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Background: People with AIDS have an elevated risk for cancer. We studied the relationship between cancer risk and AIDS-related immunosuppression as measured by CD4 count at AIDS onset.

Methods: We linked records from AIDS and cancer registries in 11 US regions (1990–1996). We studied 82,217 (86.6%) adults who had a CD4 count measured at AIDS onset and survived into the follow-up period. We calculated standardized incidence ratios (SIRs) for AIDS-defining (Kaposi sarcoma [KS], non-Hodgkin lymphoma [NHL] and cervical cancer) as well as non-AIDS-defining cancers in the 2 years after AIDS onset. For each cancer, the change in SIRs across CD4 counts (0–49 cells/mm^3, 50–99 cells/mm^3, 100–199 cells/mm^3, and ≥200 cells/mm^3) was modeled using Poisson regression.

Results: The SIRs for KS, NHL, and cervical cancer were 258, 78, and 8.8, respectively. For each fall of 100 CD4 cells/mm^3, RRs were 1.36 (95% CI: 1.29–1.43) for KS and 1.48 (95% CI: 1.37–1.59) for NHL. Among NHL subtypes, the association with lower CD4 counts was strongest for immunoblastic lymphoma (RR = 1.64, 95% CI: 1.37–1.96, per decline of 100 CD4 cells/mm^3) and central nervous system lymphoma (RR = 2.29, 95% CI: 1.95–2.69). The SIR for cervical cancer did not vary with CD4 count (p = .74). For non-AIDS-defining cancers (overall SIR = 2.1), neither the combined risk nor the risk of specific types was associated with declining CD4 counts.

Conclusions: KS and NHL risk increased with level of immunosuppression at AIDS onset. Risks for other cancers, including cervical cancer, were unrelated to CD4 counts. Elevated risks for non-AIDS cancers may be a result of lifestyle factors.

Key Words: CD4 counts—Kaposi sarcoma—Non-Hodgkin lymphoma—Cancer—AIDS—Epidemiology.

Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer occur in excess among people with AIDS and are designated as AIDS defining (1–5). Hodgkin disease; cancers of the lip, lung, anus, testis, and penis; and soft tissue sarcomas also occur in excess in people with AIDS, but evidence for their association with AIDS-related immunosuppression is not definitive (1,4,6–10). The elevated risk reported for some non-AIDS-defining cancers may be explained, in part, by confounding from exposures such as smoking, alcohol consumption, and concomitant viral infections, which are common in people with AIDS (2,11,12).

Identifying cancers that are related to immunosuppression can provide insight into the pathogenesis of AIDS-associated malignancy. To address this question, investigators have used the time relative to AIDS onset as an indicator of the degree of immune deficiency (1,2,6), but people with HIV infection progress to AIDS at different rates. (13–15). CD4 lymphocyte counts at AIDS onset are a direct measure of immune status. Three cohort studies used CD4 counts to study the relationship between immunity and cancer risk, but they were small and did not provide robust estimates (16–18).

AIDS registries provide a resource suitable for the study of cancer in persons with AIDS. The proportion of people reported to AIDS registries who have a CD4

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count measured at AIDS onset has increased through the 1990s, especially since the presence of a low CD4 count (<200 cells/mm^3) was included in the AIDS case definition in 1993 (5). We looked at the association between CD4 counts at AIDS onset and subsequent risk for cancer using data from the AIDS–Cancer Match Registry study.

METHODS

The study population has been described previously (2). Briefly, we linked AIDS and cancer registries from 11 regions in the United States (Massachusetts, Connecticut, New Jersey, Florida, Illinois, Seattle, San Francisco, Los Angeles, Atlanta, New York, and San Diego) to identify cancers arising in persons with AIDS. The present analysis was limited to adults (age of 15 years or older at AIDS onset). To increase the proportion of subjects with a recorded CD4 count, we restricted the present analysis to persons registered with AIDS in 1990 and after. No data were available after 1996. Data from one AIDS registry were excluded because CD4 counts were not provided, and KS data from another registry were excluded because of coding ambiguity in the diagnosis of KS. We classified subjects according to their CD4 count at AIDS onset (defined as −6 months to +3 months relative to the date of AIDS diagnosis) into four strata: 0–49 cells/mm^3, 50–99 cells/mm^3, 100–199 cells/mm^3, and ≥200 cells/mm^3. When several CD4 counts were available in this period, the count closest to the date of AIDS diagnosis was used.

We used data from cancer registries to identify cancers occurring in the 2-year period spanning 4 to 27 months after AIDS onset (follow-up period). Follow-up ended at death or date of last follow-up by the AIDS or cancer registries. We used the *International Classification of Diseases in Oncology* (2nd ed. [ICDO-2]) topography and morphology codes to categorize cancers (1,19). We categorized NHLs using site codes into the lymph node, central nervous system (CNS), or other NHLs. We also categorized NHLs by histology according to the Working Formulation as low grade, intermediate grade, high grade further subtyped as Burkitt or immunoblastic lymphoma, and other/unspecified grade of NHL (20,21). We excluded subjects with KS or NHL as an AIDS-defining diagnosis from our analysis of subsequent risk for those malignancies. For non-AIDS-defining cancers, only sites with 10 or more events were analyzed separately.

We used standardized incidence ratios (SIRs) to measure risk for each cancer type. SIRs were calculated as the ratio between observed (O_i) and expected cancers (E_i) for each CD4 count stratum, *i*. The expected numbers of cases for each cancer were calculated by applying registry-, sex-, race-, age-, and year-specific rates to the person-years at risk. We tested for a trend in risk for each cancer across CD4 count strata and modeled the RR using a Poisson regression model: $\ln(O_i / E_i) = a + b \times CD4_i$, where $CD4_i$ was the median CD4 count in stratum *i*. The exp(b) represents a measure of association with immune status, expressed as a relative increase in cancer incidence per decline in CD4 count of 100 cells/mm^3.

RESULTS

There were 147,596 adolescents and adults registered with AIDS, of whom 94,901 (64%) had a CD4 count at AIDS onset. Individuals with CD4 counts at AIDS onset closely resembled those without counts in terms of sex, race, age, and HIV exposure category (Table 1). Subjects were predominantly male (84%). By transmission category, 46% were homosexual men and 24% were injection drug users. The average age was 38 years. The distribution of CD4 counts at AIDS onset was 32% with counts ranging from 0 to 49 cells/mm^3, 17% with counts ranging from 50 to 99 cells/mm^3, 38% with counts ranging from 100 to 199 cells/mm^3, and 13% with counts ≥200 cells/mm^3.

A total of 82,217 (87%) subjects with CD4 counts survived at least 3 months after AIDS onset and were analyzed for cancer outcomes in the follow-up period, defined as 4 to 27 months after AIDS onset. The mortality rate in the follow-up period was inversely related to CD4 count at AIDS onset, rising from 102 per 1000 person-years among people with CD4 counts ≥200 cells/mm^3 at AIDS onset to 479 per 1000 person-years among those with 0 to 49 cells/mm^3 at AIDS onset (Table 2, p for trend < .001).

Risk for AIDS-Defining Cancers

Table 3 shows SIRs for AIDS-defining cancers by CD4 count and the RR for each decrease of 100 cells/mm^3 in CD4 counts. Overall, 1937 KS cases were observed versus 7.5 expected (SIR = 258, 95% CI: 247–270). SIRs for KS increased with declining CD4 count, ranging from 140 among subjects with a CD4 cell count ≥200 cells/mm^3 to 309 among those with 0 to 49

TABLE 1. *Characteristics of subjects with and without CD4 lymphocyte count at AIDS*

Variable	CD4 count present N = 94,901 (%)	CD4 count absent N = 52,695 (%)
Sex		
Male	78,502 (83)	44,731 (85)
Female	16,399 (17)	7,964 (15)
Race		
White	42,058 (44)	25,023 (48)
Black	35,123 (37)	19,078 (36)
Hispanic/other	17,720 (19)	8594 (16)
Exposure category		
MSM	45,585 (48)	27,780 (53)
IDU	22,506 (24)	12,261 (23)
MSM/IDU	5263 (6)	2768 (5)
Heterosexual	10,890 (12)	4888 (9)
Other	10,567 (12)	4998 (10)
Age at AIDS diagnosis, years		
15–29	15,539 (16)	8745 (16)
30–39	43,661 (46)	24,160 (46)
40–49	25,675 (27)	13,728 (26)
50–59	7316 (8)	4343 (8)
60+	2710 (3)	1719 (4)
Mean age, years (sd)	38.0 (9.6)	38.1 (9.4)

MSM, men who have sex with men; IDU, injection drug users; sd, standard deviation.

TABLE 2. *Mortality rates by CD4 lymphocyte count at AIDS*

CD4 count, cells/mm^3	Subjects with AIDS, *n*	Alive at 4 mo, *n* (%)	Person years 4–27 mo after AIDS onset	Mortality rate, per 1000 person-years	Mortality rate ratio[a]
0–49	30,478	24,781 (87)	28,147	479	4.70
50–99	16,065	13,947 (92)	17,942	320	3.14
100–199	35,943	32,494 (96)	46,023	156	1.53
200+	12,415	10,995 (95)	15,616	102	Reference

[a] p value for trend across categories of CD4 count, <.001.

cells/mm^3. KS risk increased 36% with each decline of 100 cells/mm^3 (RR = 1.36, $p < .001$; Fig. 1A).

There were 1158 cases of NHL observed in the follow-up period compared with 14.8 expected (overall SIR = 78.1, 95% CI: 73.7–82.7). The SIR for NHL increased from 44.0 among subjects with a CD4 count ≥200 cells/mm^3 at AIDS onset to 111 among those with count of 0 to 49 cells/mm^3. Correspondingly, NHL risk increased 48% with each decline of 100 cells/mm^3 (RR = 1.48, $p < .001$; see Fig. 1B). Risk increased most steeply for immunoblastic lymphoma (RR = 1.64, $p < .001$; see Fig. 1C), other/unspecified-grade lymphoma (RR = 1.50, $p < .001$), and intermediate-grade lymphoma (RR = 1.43, $p < .001$) as CD4 counts fell. No trend was observed for Burkitt lymphoma (RR = 0.91, $p = .61$, see Fig. 1D), other high-grade lymphoma (RR = 0.86, $p = .39$), or low-grade lymphoma (RR = 0.96, $p = .92$), however. Risk for NHL at all sites increased with falling CD4 counts, but the relationship was strongest for CNS NHL (RR = 2.29, $p < .001$; see Fig. 1E), intermediate for NHL of unspecified sites (RR = 1.43, $p < .001$), and weakest for nodal NHL (RR = 1.16, $p = .006$).

There were 26 cases of invasive and 77 of in situ cervical cancer in the follow-up period (overall SIRs = 8.8, 95% CI: 6.0–13.0, and 9.3, 95% CI: 7.4–11.6, respectively), but SIRs did not vary by CD4 count (see Table 3 and Fig. 1F).

Risk for Non-AIDS-Defining Cancers

Table 4 shows SIRs for non-AIDS-defining cancers by CD4 strata. Overall, 359 non-AIDS-defining cancers were observed compared with 172 expected (SIR = 2.1, 95% CI: 1.9–2.3). The SIRs for some non-AIDS-defining malignancies were elevated modestly, but none of the SIRs varied significantly by CD4 count. Lung cancer was the most frequently observed non-AIDS-defining malignancy (overall SIR = 2.8). The SIR was highest for anal cancers (overall SIR = 49.9) and Hodgkin disease (overall SIR = 11.0), but rates across CD4 categories were unstable. We observed 10 CNS tumors compared with 4.5 expected; the overall SIR was 2.2 and rose with declining CD4 counts, but the trend was not significant. Only 2 of these (both gliomas) had specified histology. The SIR for testicular cancer (both seminoma and nonseminoma) was 1.4.

TABLE 3. *Relative risk of Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer among persons with AIDS*

Cancer outcome	N	Overall SIR	SIR by CD4 lymphocyte category				RR per drop of 100 CD4 cells/mm^3 (95% CI)	p value
			200+	100–199	50–99	0–49		
KS	1937	258	140	226	368	309	1.36 (1.29–1.43)	<.001
NHL	1158	78.1	44.0	62.0	100	111	1.48 (1.37–1.59)	<.001
Grade								
High grade	279	114	60.1	102	167	134	1.35 (1.17–1.56)	<.001
Immunoblastic	201	134	39.9	114	183	190	1.64 (1.37–1.96)	<.001
Burkitt	35	103	98.9	103	212	35.0	0.91 (0.62–1.33)	.61
Other high-grade	43	72.2	89.5	70.2	101	46.6	0.86 (0.61–1.21)	.39
Intermediate grade	384	67.1	40.2	55.9	76.6	96.6	1.43 (1.26–1.62)	<.001
Low grade	12	4.2	4.4	3.9	6.2	3.2	0.96 (0.50–1.86)	.92
Other/unspecified	484	101	59.3	73.3	132	154	1.58 (1.46–1.70)	<.001
Site								
Lymph node	493	56.1	45.6	50.3	74.9	60.0	1.16 (1.04–1.29)	.006
CNS	320	175	27.2	105	217	330	2.29 (1.95–2.69)	<.001
Other	345	81.9	43.6	69.5	104	112	1.44 (1.26–1.64)	<.001
Cervical cancer, invasive	26	8.8	10.3	8.2	12.5	6.7	1.08 (0.68–1.70)	.74
Cervical cancer, in situ	77	9.3	6.4	9.4	10.5	9.7	0.88 (0.67–1.16)	.37

N, observed cases; CNS, central nervous system; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio; RR, relative risk; CI, confidence interval.

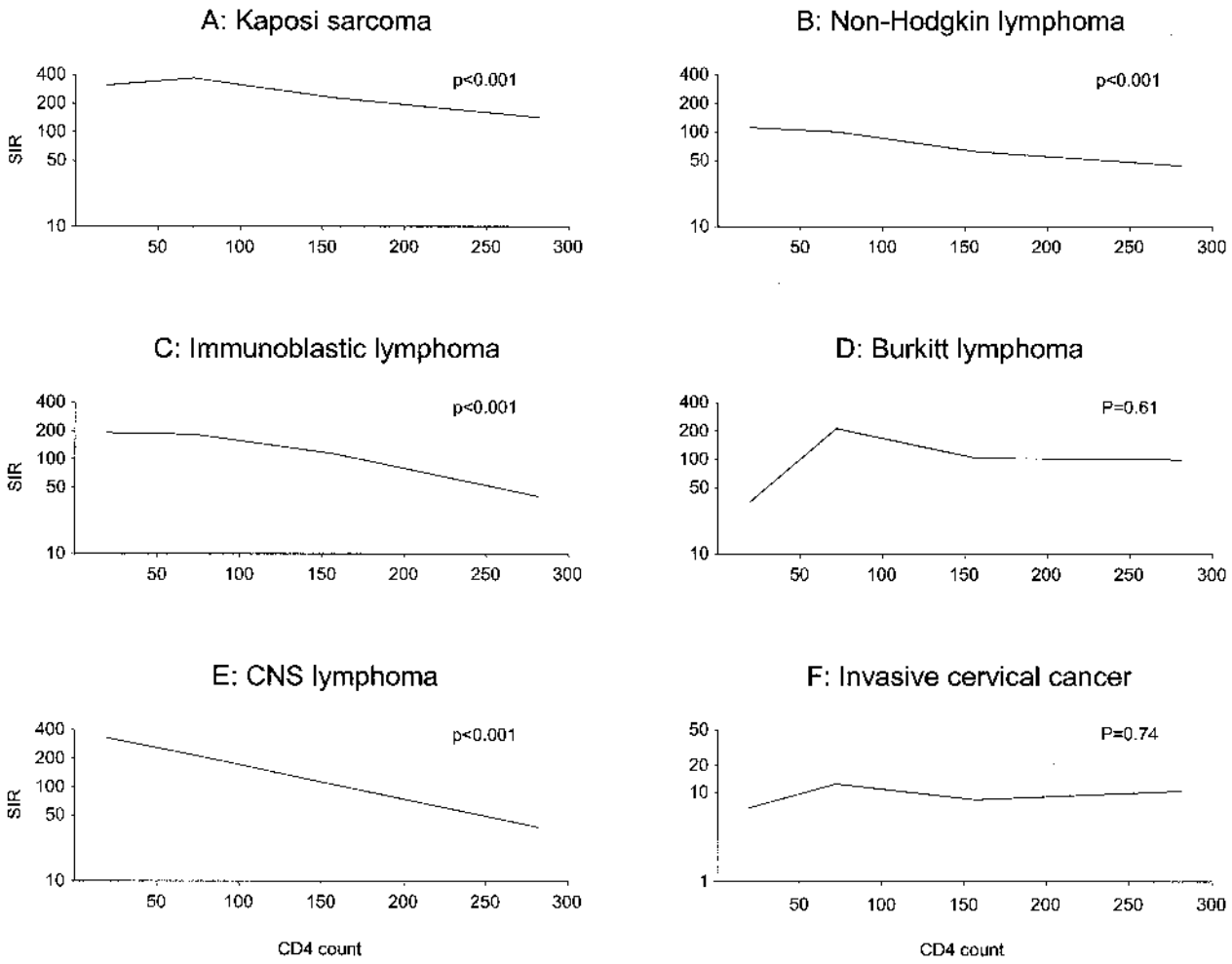

FIG. 1. Risk of cancer in persons with AIDS by CD4 count at AIDS onset. Results are shown for Kaposi sarcoma **(A)**, combined non-Hodgkin lymphoma **(B)**, immunoblastic lymphoma **(C)**, Burkitt lymphoma **(D)**, central nervous system lymphoma **(E)**, and cervical cancer **(F)**. Risk is presented on a log-transformed scale as the standardized incidence ratio (SIR) (i.e., the ratio of observed to expected cases; see Methods section). The *p* values are for trend in SIRs as a function of CD4 count. CD4 lymphocyte counts are measured in units of cells/mm^3. Note that the vertical scale in panel F differs from that in the other panels.

Several sites had a lower SIR, or the RR fell with CD4 counts (see Table 4). For oral cancers, risk declined as CD4 counts fell ($p < .001$), but the overall risk was elevated (SIR = 2.2). For prostate and breast cancer, fewer cases were observed than expected (overall SIRs = 0.5 and 0.8, respectively), but the decreases in risk were not statistically significant.

DISCUSSION

Our study is the largest to use CD4 counts to assess the relationship between immune status and cancer risk. Overall, risk for KS and NHL increased as CD4 counts declined, rising approximately 40% to 50% for each decrease of 100 cells/mm^3 among people with AIDS. Risks of cervical cancer, an AIDS-defining cancer, and of non-AIDS-defining cancers were unrelated to CD4 counts.

Of interest, for KS and several NHL subtypes, the magnitudes of the RRs associated with decreasing CD4 count were small (decline of 1.4–2.3 per 100 cells/mm^3) in comparison to the overall SIRs (e.g., 258 for KS, 134 for immunoblastic lymphoma, 175 for CNS lymphoma; see Table 3). We attribute this finding to a "threshold effect" in cancer risk. Specifically, risk for some cancers could be low in patients with a relatively preserved immune function (e.g., CD4 counts >500 cells/mm^3) but could rise steeply as CD4 counts declined below a threshold point. Our study included only people with AIDS, whose CD4 counts were almost universally low compared with the general population (only 13.1% of

TABLE 4. *Relative risk of non-AIDS-defining cancer among persons with AIDS*[a]

Site/histology	N	Overall SIR	SIR by CD4 category				RR per drop of 100 CD4 cells (95% CI)	*p* value
			200+	100–199	50–99	0–49		
All non-AIDS-defining cancers	359	2.1	2.2	2.2	2.0	1.9	0.92 (0.82–1.04)	.19
Lung	74	2.8	2.6	2.7	3.8	2.6	1.06 (0.81–1.38)	.68
Hodgkin disease	33	11.0	10.0	12.1	12.2	3.4	0.78 (0.53–1.14)	.20
Oropharynx	28	2.2	5.8	3.6	1.4	2.4	0.70 (0.61–0.79)	<.001
Anus	23	49.9	34.8	283	24.3	36.7	0.87 (0.60–1.24)	.43
Prostate	14	0.5	0.4	0.7	0.2	0.3	0.83 (0.45–1.50)	.53
Melanoma	14	1.9	2.3	1.3	2.7	1.1	0.89 (0.48–1.64)	.70
Testis	11	1.4	1.1	1.8	3.7	0.7	1.04 (0.52–2.08)	.92
Breast	10	0.8	2.4	0.6	0.5	0.7	0.56 (0.27–1.13)	.10
CNS tumors	10	2.2	1.5	1.0	2.6	4.7	2.06 (0.87–4.87)	.10

[a] Only cancers with 10 or more events in the 4–27 months after AIDS onset were analyzed separately.
N, observed cases; CNS, central nervous system; SIR, standardized incidence ratio; RR, relative risk; CI, confidence interval.

subjects had CD4 counts >200 cells/mm^3). Thus, we were not able to determine where such a threshold effect might begin. A threshold is probably relevant for Burkitt lymphoma and Hodgkin disease, both of which have been reported to occur at median CD4 counts well above 200 cells/mm^3 (22–24). This explanation is consistent with studies reporting that Burkitt lymphoma occurs less frequently secondary to another AIDS diagnosis compared with other NHL subtypes (23,25).

The mechanism through which lowered immunity increases risk for cancer risk is unclear (4). KS and primary effusion lymphoma (PEL), a rare NHL subtype, are etiologically linked to KS-associated herpesvirus (KSHV) infection (26–28). KSHV is present in KS tumor cells, and KSHV genome encodes proteins (e.g., v-cyclin and LANA) that may disrupt cell cycle control (29,30). KSHV also encodes for cytokine homologues (e.g., v-IL-6); when expressed by infected cells, these cytokine homologues may cause precursor cells to proliferate and transform some of them into neoplastic spindle cells (30). No genetic abnormalities have been consistently documented in KS spindle cells, however, and KS can resolve following immune reconstitution (31). PELs are invariably associated with KSHV, but unlike KS, they generally display genetic abnormalities. NHLs likely arise following polyclonal expansion of B lymphocytes in the setting of poor regulation by dysfunctional T lymphocytes. African Burkitt lymphoma is convincingly linked to Epstein-Barr virus (EBV) in HIV-uninfected individuals (32,33). In HIV infection, EBV is frequently found in several NHL subtypes (immunoblastic lymphoma, CNS lymphoma) but not as often in other lymphomas (including Burkitt lymphoma). EBV, like KSHV, encodes proteins that could be responsible for stimulating cellular proliferation (34). In our study, immunoblastic lymphoma and CNS lymphoma (most of which have immunoblastic histology and are associated with EBV) showed the strongest associations with declining CD4 counts.

SIRs for both invasive and in situ cervical cancer were elevated. HIV-infected women have a higher prevalence of cervical infection with human papillomavirus, the etiologic agent for cervical cancer, than do HIV-uninfected women (35), which partly accounts for their increased risk. Frisch et al. (1) found that risk for in situ cervical cancer increased during the pre-AIDS period but remained level after AIDS onset. This observation suggests that immunity could be important for the clearance of early-stage preneoplastic lesions, although the relationship could also be affected by factors related to health care and access to screening. Although we did not find a trend between in situ cervical cancer and CD4 counts, we cannot exclude an immunologic threshold as the explanation for the elevated risk.

Although we observed an overall excess risk for many cancers in people with AIDS compared with the general population, a trend with worsening immunity was demonstrated only for KS and immunoblastic lymphoma. Confounding from lifestyle factors may partly explain the excess risk for some of these cancers. Exposures such as smoking, alcohol consumption, and sexually transmitted diseases are common among people with AIDS (2,11,12).

This is the largest study to use CD4 count as a direct measure of immune deficiency and risk for cancer. Nevertheless, the following limitations should be considered. CD4 counts were not available for all people, but we found no obvious biases in the 36% of people without CD4 counts. Because we studied cancers occurring in the 2-year period after AIDS onset, when people are severely immunosuppressed, we cannot exclude a relationship with immunity appearing earlier or at higher CD4 counts (a threshold effect). To determine a threshold effect requires studies of cancer risk across the whole spectrum

of CD4 counts, a study that would be best done on persons followed from the onset of HIV infection (10) rather than at AIDS onset. We had no data after 1996, so immune reconstitution related to highly active antiretroviral therapy (HAART) is not likely to have biased our results. Therefore, our study cannot address the relationship between CD4 counts and cancer risk during HAART. Finally, we cannot exclude biases arising from underascertainment of cases in severely immunosuppressed individuals. People who are extremely sick from other conditions may not be evaluated for cancer. Underascertainment could partly explain the drop in SIR for Burkitt lymphoma and Hodgkin disease in the lowest CD4 count category. The apparent deficit in breast and prostate cancers could be a result of underdiagnosis, underreporting, or competing mortality.

To summarize, we found associations with immunosuppression for KS and for most subtypes of AIDS-associated NHL. Nevertheless, the incidence of other cancers, including cervical cancer, did not show a trend with decline in CD4 count in our study.

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